

**WEST**

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File: USPT

Feb 12, 2002

DOCUMENT-IDENTIFIER: US 6346512 B1

TITLE: Compounds and methods for modulating cell adhesion

Detailed Description Text (10):

As noted above, multiple CAR sequences may be present within a modulating agent. CAR sequences that may be included within a modulating agent are any sequences specifically bound by an adhesion molecule. As used herein, an "adhesion molecule" is any molecule that mediates cell adhesion via a receptor on the cell's surface. Adhesion molecules include members of the cadherin gene superfamily that are not classical cadherins (e.g., proteins that do not contain an HAV sequence and/or one or more of the other characteristics recited above for classical cadherins), such as desmogleins (Dsg) and desmocollins (Dsc); integrins; members of the immunoglobulin supergene family, such as N-CAM; and other uncategorized transmembrane proteins, such as occludin, as well as extracellular matrix proteins such as laminin, fibronectin, collagens, vitronectin, entactin and tenascin. Preferred CAR sequences for inclusion within a modulating agent include (a) Arg-Gly-Asp (RGD), which is bound by integrins (see Cardarelli et al., J. Biol. Chem. 267:23159-64, 1992); (b) Tyr-Ile-Gly-Ser-Arg (YIGSR; SEQ ID NO:52), which is bound by .alpha.6.beta.1 integrin; (c) KYSFNYDGSE (SEQ ID NO:53), which is bound by N-CAM; (d) the N-CAM heparin sulfate-binding site IWKHKGRDVILKKDVR (SEQ ID NO:54); (e) the occludin CAR sequence LYHY (SEQ ID NO:55); (f) claudin CAR sequences comprising at least four consecutive amino acids present within a claudin region that has the formula: Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:56), wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and (g) nonclassical cadherin CAR sequences comprising at least three consecutive amino acids present within a nonclassical cadherin region that has the formula: Aaa-Phe-Baa-Ile/Leu/Val-Asp/Asn/Glu-Caa-Daa-Ser/Thr/Asn-Gly (SEQ ID NO:57), wherein Aaa, Baa, Caa and Daa are independently selected amino acid residues; Ile/Leu/Val is an amino acid that is selected from the group consisting of isoleucine, leucine and valine, Asp/Asn/Glu is an amino acid that is selected from the group consisting of aspartate, asparagine and glutamate; and Ser/Thr/Asn is an amino acid that is selected from the group consisting of serine, threonine or asparagine. Representative claudin CAR sequences include IYSY (SEQ ID NO:58), TSSY (SEQ ID NO:59), VTAF (SEQ ID NO:60) and VSAF (SEQ ID NO:61). Representative nonclassical cadherin CAR sequences include the VE-cadherin (cadherin-5) CAR sequence DAE; the cadherin-6 CAR sequences EEY, NEN, ESE and DSG; the cadherin-7 CAR sequences DEN, EPK and DAN; the cadherin-8 CAR sequences EEF and NDV; the OB-cadherin (cadherin-11) CAR sequences DDK, EEY and EAQ; the cadherin-12 CAR sequences DET and DPK; the cadherin-14 CAR sequences DDT, DPK and DAN; the cadherin-15 CAR sequences DKF and DEL; the PB-cadherin CAR sequences EEY, DEL, DPK and DAD; the protocadherin CAR sequences DLV, NRD, DPK and DPS; the dsg CAR sequences NQK, NRN and NKD; the dsc CAR sequences EKD and ERD and the cadherin-related neuronal receptor CAR sequences DPV, DAD, DSV, DSN, DSS, DEK and NEK.

Detailed Description Text (47):

As noted above, a modulating agent may consist entirely of one or more cyclic peptides, or may contain additional peptide and/or non-peptide sequences, which may be linked to the cyclic peptide(s) using conventional techniques. Peptide portions may be synthesized as described above or may be prepared using recombinant methods. Within such methods, all or part of a modulating agent can be synthesized in living

cells, using any of a variety of expression vectors known to those of ordinary skill in the art to be appropriate for the particular host cell. Suitable host cells may include bacteria, yeast cells, mammalian cells, insect cells, plant cells, algae and other animal cells (e.g., hybridoma, CHO, myeloma). The DNA sequences expressed in this manner may encode portions of an endogenous cadherin or other adhesion molecule. Such sequences may be prepared based on known cDNA or genomic sequences (see Blaschuk et al., J. Mol. Biol. 211:679-682, 1990), or from sequences isolated by screening an appropriate library with probes designed based on the sequences of known cadherins. Such screens may generally be performed as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y., 1989 (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using oligonucleotide primers in methods well known in the art, to isolate nucleic acid molecules encoding all or a portion of an endogenous adhesion molecule. To generate a nucleic acid molecule encoding a peptide portion of a modulating agent, an endogenous sequence may be modified using well known techniques. For example, portions encoding one or more CAR sequences may be joined, with or without separation by nucleic acid regions encoding linkers, as discussed above. Alternatively, portions of the desired nucleic acid sequences may be synthesized using well known techniques, and then ligated together to form a sequence encoding a portion of the modulating agent.

## WEST Search History

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<u>Set Name</u> side by side	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u> result set
<i>DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR</i>			
L21	(isoleucine) same (adhes\$ or adhere or bind\$) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	142	L21
L20	(isoleucine) same (adhes\$ or adhere or bind\$) and (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	1761	L20
L19	(isoleucine) same (adhes\$ or adhere) adj10 (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	2	L19
L18	(isoleucine) same (adhes\$ or adhere) adj5 (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	2	L18
L17	(isoleucine) same (adhes\$ or adhere) same (microb\$ or bacteri\$ or yeast or fungal)	3	L17
L16	(isoleucine) same (adhes\$ or adhere) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	3	L16
L15	isoleucine and (microbe or microbial or bacteria) same adhere	117	L15
L14	isoleucine same (microbe or microbial or bacteria) same adhere	1	L14
L13	isoleucine adj10 (microbe or microbial or bacteria) same adhere	0	L13
L12	isoleucine adj8 microbe same adhere	0	L12
L11	L10 and isoleucine same (adhere or adhesion or adhesive)	26	L11
L10	L7 and infection	3188	L10
L9	L8 and isoleucine adj8 (adhere or adhesion or adhesive)	4	L9
L8	L7 and (powder or ointment or paste or cream)	2830	L8
L7	isoleucine and (adhesion or adhere)and (microbe or microbial or microbacteria or bacteria)	4033	L7
L6	isoleucine same (adhesion or adhere)and (microbe or microbial or microbacteria or bacteria)	39	L6
L5	isoleucine same (powder or paste or ointment or cream) same (infection or microbial)	16	L5
L4	isoleucine and (powder or paste or ointment or cream) same (infection or microbial)	389	L4
L3	isoleucine and (powder or paste or ointment or cream) and (infection or microbial)	8248	L3
L2	L1 and (powder or paste or ointment or cream)	51	L2
L1	(microbe or microbial) same isoleucine	165	L1

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Terms	Documents
(isoleucine) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma) same (adhes\$ or adhere)	3

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 or yeast or fungal or

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<u>L25</u>	(isoleucine) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma) same (adhes\$ or adhere)	3	<u>L25</u>
<u>L24</u>	(isoleucine) same (adhes\$ or adhere or anti-adhesive or adhesion adj3 inhibit\$) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	3	<u>L24</u>
<u>L23</u>	(isoleucine) same (adhes\$ or adhere or block\$) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	33	<u>L23</u>
<u>L22</u>	(isoleucine) same (adhes\$ or adhere or stick) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	3	<u>L22</u>
<u>L21</u>	(isoleucine) same (adhes\$ or adhere or bind\$) same (microb\$ or bacteri\$ or yeast or fungal or mycoplasma)	142	<u>L21</u>

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